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Serum levels of IL-6, IL-8, and IL-10 are indicators of prognosis in pancreatic cancer

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Abstract

Objective: Early detection and prognosis prediction are critical to improve patient survival in pancreatic cancer. This study aimed to investigate whether interleukins could serve as indicators of prognosis in pancreatic cancer.

Methods: Sixty-eight patients with pancreatic cancer were enrolled in the study during the period between 2012 and 2014. The serum levels of a broad spectrum of interleukins in these patients were determined, including IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IL-15, and IL-23.

Results: IL-6, IL-8, and IL-10 showed significant positive correlations with each other. Moreover, high levels of serum IL-6, IL-8, and IL-10 were independently strongly associated with poor survival of patients with pancreatic cancer.

Conclusions: Our results suggest that serum levels of IL-6, IL-8, and IL-10 could be useful markers for prediction of prognosis in patients with pancreatic cancer.

Keywords

Pancreatic cancer, interleukin, IL-6, IL-8, IL-10, prediction marker

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Introduction

Pancreatic cancer is the fourth most common cause of cancer-related mortality in Europe and the United States;[1] its fatality rate is nearly 100%, which is likely because of the difficulty of early diagnosis, as well as high rates of metastasis and

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therapeutic resistance.[2,3] Moreover, its 5-year survival rate is approximately 5%, and the median survival period is less than 6 months for most patients.[3] Pancreatic cancer is estimated to become the second leading cause of cancer death in the United States by 2020.[4] Early detection and prediction of prognosis are critical for improving patient survival in pancreatic cancer.

The interleukins are an important group of cytokines, many of which play crucial roles in transmission of information, regulation of immune cell activation, and regulation of the inflammatory response. It has been reported that many interleukins are associated with the promotion of metastasis and angiogenesis, poor prognosis, and immune evasion; these include pro-inflammatory and anti-inflammatory cytokines, such as IL-1β, IL-6, IL-8, and IL-10.[5–11] Notably, increasing evidence suggests that changes in interleukin expression are associated with poor prognosis in advanced pancreatic cancer.[8,9]

In this study, we examined serum levels of a broad spectrum of interleukins in 68 patients with pancreatic cancer—including IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IL-15, and IL-23—in order to investigate the association between interleukins and poor prognosis in pancreatic cancer.

Materials and methods

Patients

Patients with pancreatic cancer who were treated in Fudan University Shanghai Cancer Center (FUSCC) were enrolled in our study. Patients with immunosuppressive diseases and immunosuppressive drugs were excluded from the present study. The Clinical Research Ethics Committee of FUSCC approved this study (050432-4-1212B) and all patients provided written informed consent. Relevant clinicopathological features, such as age, sex, tumor location, and TNM stage, were recorded for each patient. Clinicopathological features were classified by using the criteria of the Union for International Cancer Control (UICC) (seventh edition). Overall survival (OS) was defined as the time from the diagnosis to the date of death or last contact.

Interleukin assays

Five milliliters of peripheral venous blood were taken from the patient's arm; serum was collected by centrifugation for 15 minutes at $1000 \times g$, then stored at $-80^{\circ}C$ until use. The serum levels of interleukins (IL-1β, IL-2, IL-6, IL-8, IL-10, IL-13, IL-15, and IL-23) were measured by using the Q-Plex multiplex array (Quansys Biosciences, Logan, UT, USA) on a Q-View Imager (Quansys Biosciences), in accordance with the manufacturer's protocol. Briefly, a series of 1:2 dilutions were made of various interleukins with known concentrations, in order to generate a calibration curve. Fifty microliters of calibrators and samples per well were added into the Q-Plex™ Array 96-well plate and incubated for 1 hour at room temperature; the plate was then washed and incubated with detection mix for 1 hour at room temperature. Next, the plate was successively incubated with streptavidin-HRP and substrate mix for 15 minutes each at room temperature. Finally, the plate was imaged by using a 270-second exposure time on a Q-View™ Imager LS. Interleukin concentrations were analyzed by Q-View™ software.

Statistical analyses

Correlations of clinicopathological parameters and interleukin expression levels were analyzed by using Spearman's χ^2 test. Survival curves were calculated by the Kaplan-Meier method and compared by

log-rank tests. The Cox multivariate model was used to assess the relationships between risk factors and survival. Data were analyzed with IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA). Statistical significance was set at $p<0.05$.

Results

Patient characteristics

Sixty-eight patients with pancreatic cancer were enrolled in the study between 2012 and 2014. Among those patients, 23 were female, while 45 were male. The tumor stages comprised 23 cases of TNM III (33.8%) and 45 cases of TNM IV (66.2%); the tumor was located in the head and neck of the pancreas in 29 patients (42.6%), and in the body and tail of the pancreas in 39 patients (57.4%). The ages of the patients ranged from 28 to 82 years old; most were between 55–60 years old (Figure 1a). In addition, the survival periods of most patients (75%) were less than 1 year (Figure 1b).

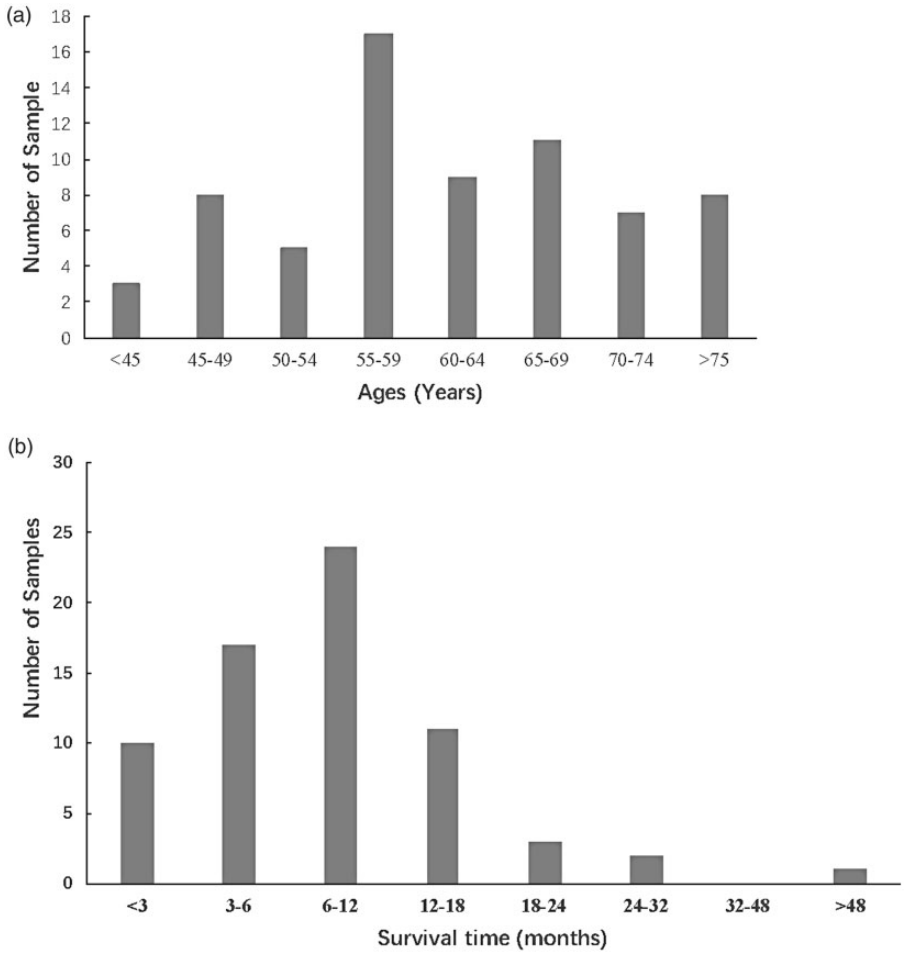

Figure 1. General characteristics of age and overall survival among all patients.

Interleukin expression levels

Levels of each interleukin were evaluated in all 68 patients; serum interleukin concentrations are shown in Figure 2. We explored the associations between survival time and interleukin expression levels; only levels of IL-6, IL-8, and IL-10 showed significant correlations with survival time ($p<0.001$ for all) (Table 1). Additionally, we examined the relationships between interleukin levels (IL-6, IL-8, and IL-10) and clinicopathological features, including sex, age, tumor location, and TNM stage; importantly, no significant correlations were found (Table 2). Intriguingly, IL-6, IL-8, and IL-10 showed significant correlations with each other ($p<0.001$ for all) (Table 3).

Relationships between patient prognosis and levels of IL-6, IL-8, and IL-10

To further investigate the correlations between the levels of IL-6, IL-8, and IL-10 and the survival of pancreatic cancer patients, we performed univariate Cox analysis and Kaplan-Meier curves with log-rank analysis for OS. Patients with high IL-6, IL-8, or IL-10 expression (greater than median expression levels) exhibited

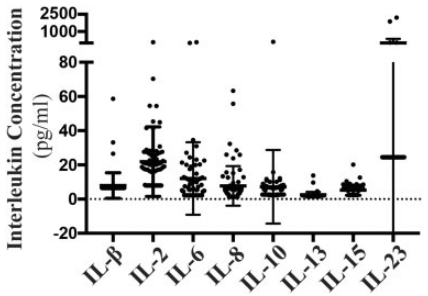

Figure 2. Serum interleukin concentrations in patients with pancreatic cancer. Standard deviation (SD) is shown as error bars.

Table 2. Relationships between expression of IL-6, IL-8, and IL-10 and various clinicopathological features.

	IL-6	IL-8	IL-10
TNM stage			
Correlation coefficient	0.16	0.134	0.157
Sig.	0.195	0.277	0.201
Sex			
Correlation coefficient	0.077	0.021	−0.015
Sig.	0.536	0.862	0.905
Age			
Correlation coefficient	0.141	−0.044	0.136
Sig.	0.254	0.719	0.267
Survival time			
Correlation coefficient	−0.516**	−0.414**	−0.431**
Sig.	<0.001	<0.001	<0.001
Location			
Correlation coefficient	0.08	0.181	−0.02
Sig.	0.52	0.139	0.872

Table 3. Correlations among expression levels of IL-6, IL-8, and IL-10.

	IL-6	IL-8	IL-10
IL-6			
Correlation coefficient	1	0.541**	0.579**
Sig.		<0.001	<0.001
IL-8			
Correlation coefficient	0.541**	1	0.515**
Sig.	<0.001		<0.001
IL-10			
Correlation coefficient	0.579**	0.515**	1
Sig.	<0.001	<0.001	

Table 1. Relationships between cytokine expression and survival time.

	IL-1β	IL-2	IL-6	IL-8	IL-10	IL-13	IL-15	IL-23
Survival time								
Correlation coefficient	0.047	−0.02	−0.516**	−0.414**	−0.431**	0.021	−0.158	0.046
Sig.	0.706	0.87	<0.001	<0.001	<0.001	0.867	0.199	0.707

a significantly shorter survival time, compared with patients with low expression (less than median expression levels) ($p<0.001$ for IL-6, $p<0.01$ for IL-8, and $p<0.05$ for IL-10) (Figure 3). Univariate Cox analysis revealed that a high expression level of either IL-6, IL-8, or IL-10 was associated with poor survival (IL-6: HR = 0.204, 95% CI: 0.107–0.410, $p<0.001$; IL-8: HR = 0.303, 95% CI: 0.135–0.683, $p<0.01$; IL-10: HR = 0.336, 95% CI: 0.125–0.900, $p<0.05$) (Table 4 and Figure 3).

Discussion

Pancreatic cancer is a highly malignant digestive system tumor with rapid progression and poor prognosis.[4] Therefore, the identification of predictive markers for patient prognosis is critical for therapeutic approach in pancreatic cancer. In this study, we found that serum expression levels of IL-6, IL-8, and IL-10 were associated with OS in patients with pancreatic cancer. High levels of IL-6, IL-8 or IL-10 were positively correlated with poor prognosis in pancreatic cancer.

IL-6 is an important interleukin secreted by macrophages, T cells, and B cells, as well as many other cells; notably, it can act as either a pro-inflammatory cytokine or an anti-inflammatory myokine.[12] It can regulate immune response, acute phase response, and hematopoietic function; furthermore, it can play an important role in the body's anti-infection and immune response. Dysregulation of IL-6 expression can cause many diseases, and its clinical

Table 4. Univariate analyses for overall survival according to interleukin levels in patients with pancreatic cancer.

			95.0% CI for Exp (B)	
	p value	Exp (B)	Lower	Upper
High level of IL-6	0	0.211	0.097	0.462
High level of IL-8	0.036	0.35	0.131	0.933
High level of IL-10	0.03	0.336	0.125	0.9

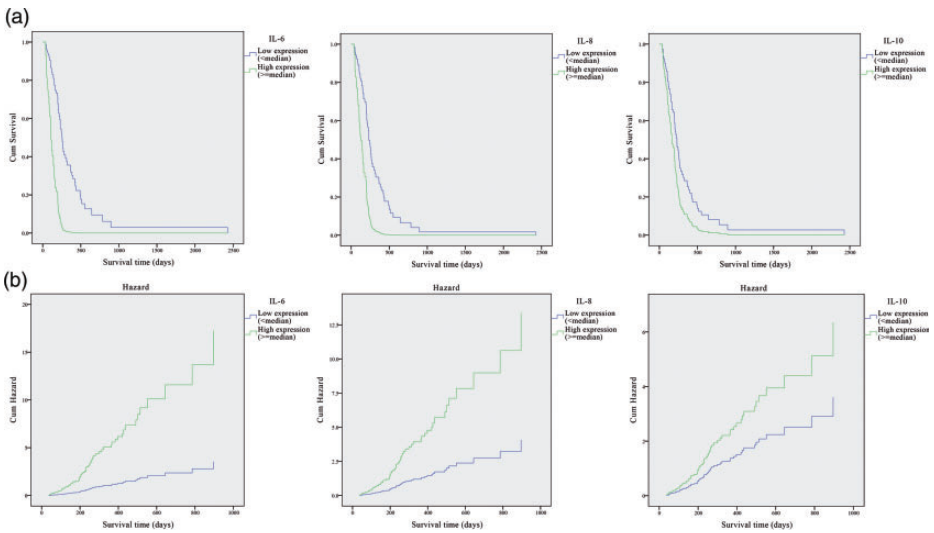

Figure 3. IL-6, IL-8, and IL-10 levels were associated with overall survival (OS) in patients with pancreatic cancer. Kaplan-Meier curves (a) and Hazard ratios (b) for OS for all cases. The median level for each group was selected as the cut-off.

manifestations primarily include elevated IL-6 levels at the onset of disease.[13,14] Elevated IL-6 levels are associated with tumor development, degree of rejection, and treatment outcome.[15–18] In addition, previous studies have revealed that IL-6 level is an potential prognostic factor in pancreatic cancer,[19] renal cell cancer,[20] and ovarian cancer;[21,22] moreover, serum levels of IL-6 and IL-1β can predict the efficacy of gemcitabine in patients with advanced pancreatic cancer.[23] In this study, we found that a high level of serum IL-6 was correlated with shorter survival and worse prognosis in pancreatic cancer. However, serum levels of IL-1β did not show a significant correlation with poor patient survival in our study.

IL-8 is an important mediator of inflammatory diseases, which plays an important role in anti-infection, immune response, and tumor suppression. IL-8 also has strong chemotactic effects on specific and nonspecific immune cells; these primarily comprise chemotactic and activating effects on neutrophils, as well as chemotactic effects on lymphocytes and basophils. As a major inflammatory factor, significantly elevated levels of IL-8 are found at sites of inflammation and serum in the presence of infection and certain autoimmune diseases.[24] IL-8 also functions in the proliferation of normal cells and tumor cells. Recent studies have shown that IL-8 can promote the development of various cancers, such as pancreatic cancer, nasopharyngeal tumor, colorectal cancer, and lung cancer;[25–28] notably, it serves as a prognostic marker in several cancers.[29–31] Consistent with previous studies, the present study showed that a high level of serum IL-8 was predictive of shorter survival times and poor prognosis in pancreatic cancer.

IL-10 is a negative regulatory factor, primarily secreted by Th2 cells, activated B cells, monocytes, and macrophages; it is involved in immune response, tumor development, and other biological regulation.[32] Importantly, IL-10 also plays a role in autoimmune diseases, serious infectious diseases, and transplantation immunity; IL-10 acts as a growth factor in certain tumor cells (e.g., myeloma cells), and maintains cell growth and proliferation.[33,34] IL-10 has been reported to serve at the crossroads of immune stimulation and immune suppression in cancer, as well as development of tumor metastasis.[35–37] A high level of serum interleukin-10 was associated with poor prognosis in multiple myeloma[38] and thyroid cancer.[39] Similarly, we found that a high level of serum IL-10 was associated with poor prognosis in pancreatic cancer.

IL-6, IL-8, and IL-10 are all involved in the inflammatory response; we found that, in patients with pancreatic cancer, the expression levels of these three interleukins were significantly positively correlated with each other, implying a role for inflammation in the development of pancreatic cancer. Chronic pancreatitis is closely correlated with pancreatic cancer in clinical analyses. A prior study analyzed 1663 patients with pancreatic cancer and found that the risk of pancreatic cancer increased by 7.2-fold among patients with pancreatitis; this risk increased by up to 10-fold in patients older than 55 years of age.[40] Similarly, our results showed a significant positive correlation between high levels of IL-6, IL-8, or IL-10 and poor prognosis in patients with pancreatic cancer. Thus, attenuation of the inflammatory response through inhibition of the expression of important inflammatory factors, such as IL-6, IL-8, or IL-10, may improve patient prognosis.

IL-13, IL-15, and IL-23 have been suggested as potential independent prognostic factors for OS in several cancers.[41–43] However, none of these interleukins showed significant correlations with the OS of patients with pancreatic cancer in

the present study. Nevertheless, certain limitations must be considered in future studies. The main limitation of the present study was the limited number of patients, which may influence the statistical evaluation and strength of correlations between serum levels of interleukins and OS. A larger sample size is necessary to confirm the reliability of the present findings.

Taken together, our results suggested that high levels of serum IL-6, IL-8, or IL-10 were strongly associated with poor survival, and that these cytokines can be regarded as useful markers to predict prognosis in patients with pancreatic cancer, as well as potential therapeutic targets.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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